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New Chiral TADDOLs for the Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by Ti(IV)

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Optically Active Ligands, Enantioselective Alkylation, Titanium Complexes

The new chiral ligands (4R, 5R)-2,2-dimethyl-a,a,a',a'-tetra(p-N,N-dimethylaminophenyl)-1,3-dioxolane-4,5-dimethanol and [(4R, 5R)-2,2-dimethyl-a,a,a',a'-tetra(p-triphenylphosphoniumphenyl)-1,3-dioxolane-4,5-dimethanol], X, (X = I, BPh4) have been synthesized and characterized. Their catalytic efficiency has been tested in the reaction of benzaldehyde and diethylzinc in the presence of Ti(OPr)4. Enantioselectivities up to S/R = 98.7:1.3 have been observed.

Results and Discussion

(4R, 5R)-2,2-Dimethyl-a,a,a',a'-tetra(p-N,N-dimethylaminophenyl)-1,3-dioxolane-4,5-dimethanol (I) was prepared by the Grignard route from dimethyl-2,3-O-isopropylidenel-L-tartrate and 4-bromo-N,N-dimethylaniline (Scheme 1). (4R, 5R)-2,2-Dimethyl-a,a,a',a'-tetra(p-triphenylphosphoniumphenyl)-1,3-dioxolane-4,5-dimethanol iodide (IIa) was obtained via (4R, 5R)-2,2-dimethyl-a,a,a',a'-tetra-p-bromophenyl-1,3-dioxolane-4,5-dimethanol (II), the product of the reaction of dimethyl 2,3-O-isopropylidenel-L-tartrate and p-bromophenylmagnesium bromide in dry ether (Scheme 1). Metathesis of IIIa and sodium tetraphenylborate afforded (4R, 5R)-2,2-dimethyl-a,a,a',a'-tetra(p-triphenylphosphoniumphenyl)-1,3-dioxolane-4,5-dimethanol tetraphenylborate (IIIb). Solid IIIb contains water which is identified by its 1H NMR signal at δ = 1.54 after dissolution in CDCl3.

I is soluble in organic solvents such as toluene, ether, THF, acetone, and ethanol. IIIa is soluble in alcoholic solvents and insoluble in THF. IIIb is readily soluble in THF and insoluble in alcohols. In addition, both IIIa and IIIb are soluble in acetone, methylene chloride, and chloroform.

It is to be expected that the substituents at the α-phenyl rings of the dioxolenedimethanol skeleton modulate both the acidity of the OH groups of the TADDOLs and the Lewis acidity of their Ti(IV) complexes. Compared to TPDDOL, the tetraphenolphosphonium groups in IIIa and IIIb will be electron-attracting, whereas the dimethylamino group will be electron-donating.

The catalytic enantioselective addition of Et2Zn to benzaldehyde in the presence of Titanium(IV) and an chiral ligand was carried out as described by
[(41.3%) of I, m.p. 232-234 °C, \([\alpha]_D^{20} = -69.0 \) (1, acetone).

C_{39}H_{90}N_{2}O_{4} (638.81)

Calcd C 73.33 H 7.89 N 8.77%

Found C 73.14 H 7.89 N 8.74%

MS (FAB): \(m/z = 637.6 \) (M–H\(^+\)), 621.6 (M–OH\(^+\)), 553.5, 500.6, 461.4, 370.4, 352.4, 323.4, 311.2, 277.3, 253.3. \(-1^H\) NMR (250 MHz, CDCl\(_3\)): \(\delta = 7.19-7.40 \) (m, 8 H, arom. H), 6.58-6.70 (m, 8 H, arom. H), 4.52 (s, 2 H, HC\(_{4,5}\)), 3.92 (s, 2 H, 2 OH), 2.90 (d, 24 H, 8 NCH\(_3\)), 1.08 (s, 6 H, 2 CCH\(_3\)).

(4 R, 5 R)-2,2-Dimethyl-\(a, a, a', a'\)-tetra-\(p\)-bromophenyl-1,3-dioxolane-4,5-dimethanol (II): From di­methyl 2,3-O-isopropylidene-L-tartrate and \(p\)-bromophenylmagnesium bromide [15] in dry ether.

Methyl 2,3-O-isopropylidene-L-tartrate and \(p\)-bromophenyl-1,3-dioxolane-4,5-dimethanol (II): From di­methyl 2,3-O-isopropylidene-L-tartrate and \(p\)-bromophenylmagnesium bromide [15] in dry ether. The mixture was stirred at room temperature for 5 h. Then, the reaction mixture was poured into 50 ml of an aqueous solution containing 0.3 g (2 mmol) of NaI, and extracted with 20 ml of ether. The ether layer was discarded and the remaining mixture was extracted three times with 10 ml of CHCl\(_3\). The CHCl\(_3\) phase was dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was dissolved in ethanol and precipitated with ethyl acetate. Recrystallization with methylene chloride-ethyl acetate afforded 0.1 g (62.5% yield) of a slightly yellow powder, m.p. 240 °C (dec.), \([\alpha]_D^{20} = -30 \) (1, acetone).

MS (FAB): \(m/z = 783, 781 \) (M–H\(^+\)), 779, 777, 740, 702, 701, 699, 667, 623, 459, 341. \(-1^H\) NMR (250 MHz, CDCl\(_3\)): \(\delta = 7.11-7.50 \) (m, 16 H, arom. H), 4.44 (s, 2 H, HC\(_{4,5}\)), 4.01 (br, 2 H, 2 OH), 1.10 (s, 6 H, 2 CH\(_3\)).

(4 R, 5 R)-2,2-Dimethyl-\(a, a, a', a'\)-tetra-\(p\)-triphenylphosphoniumphenyl)-1,3-dioxolane-4,5-dimethanol tetraphenyldiborate (IIIb): To an ethanolic solution of 0.2 g (0.1 mmol) of IIIa was added an ethanolic solution of 0.17 g (0.5 mmol) of Na tetr phenyl diborate with stirring. After 2 h, the mixture was filtered and the residue was dissolved in CH\(_2\)Cl\(_2\). Precipitation with EtOH afforded 0.27 g (96.8% yield) of a slightly yellow powder, m.p. 175 °C, \([\alpha]_D^{20} = -37 \) (1, acetone).

C_{196}H_{166}B_{4}O_{4}P_{4}•4H_{2}O (2860.69)

Calcd C 83.55 H 6.13%

Found C 83.13 H 5.85%

MS (FAB): \(m/z = 2469.4 \) (M–BPh\(_4\)-4H\(_2\)O\(^+\)), 2469.1, 2408.0, 2353.1, 2295.1, 2242.2, 2211.5, 1969.6, 1573.4, 1470.0–\(31^P\) NMR (101.262 MHz, CDCl\(_3\)): \(\delta = 23.09 \) (m, \(-1^H\) NMR (250 MHz, CDCl\(_3\)): \(\delta = 6.60-7.65 \) (m, 156 H, arom. H), 4.71 (s, 2 H, HC\(_{4,5}\)), 4.46 (br, 2 H, 2 OH), 1.54 (br, 8 H, 4 H\(_2\)), 1.25 (s, 6 H, 2 CH\(_2\)).

General procedure for catalytic reactions

To 0.16 mmol of IIIb under nitrogen was added 0.19 mmol of Ti(O\(_2\)Pr)\(_4\), 5 ml of THF and 5 ml of toluene. The mixture was stirred at room temperature for 5 h. Then, the solvent was removed at 40 °C. To the residue was added 6 ml of THF and 2.81 mmol of Ti(O\(_2\)Pr)\(_4\). The mixture was cooled to −75 °C and then 2.9 mmol of Et\(_2\)Zn was syringed. After stirring at −20 °C for 30 min the mixture was cooled to −75 °C and 2.4 mmol of freshly distilled benzaldehyde was added. The mixture was warmed up to room temperature slowly and stirred for 20 h.

The reaction was quenched by addition of 15 ml of an aqueous solution saturated with NH\(_4\)Cl. The product was isolated by usual workup [7] and further purified by bulb to bulb distillation.

Determination of the enantiomeric purity of 1-phenylpropan-1-ol: 3 drops of product, 15 drops of tert-butylylsocyanate and 1 drop of triethylamine were placed in a reaction vial and heated at 60 °C for 1h. The excess of reagents was removed by a stream of nitrogen. To the residue was added 1 ml of methylene chloride, and the enantiomeric purity was analyzed by GC. Conditions: Chirasil-Val-L column (25 m); injector temp. 225–250 °C; column temp. 110 °C; 1.0 to 5.0 ml H\(_2\)/min; retention time: 11.8 min for the (R) and 12.6 min for the (S) de­rivatives.

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